

WHAT IS CLAIMED IS:

1           1. A method of identifying a gene or genes associated with a selected  
2 phenotype, the method comprising the steps of:

3           (a) providing a nucleic acid library comprising nucleotide sequences that  
4 encode at least partially randomized zinc finger proteins;

5           (b) transducing cells with expression vectors, each comprising a nucleotide  
6 sequence from the library;

7           (c) culturing the cells so that zinc finger proteins are expressed in the cells,  
8 wherein the zinc finger proteins modulate gene expression in at least some of the cells;

9           (d) assaying the cells for a selected phenotype and determining whether or  
10 not the cells exhibit the selected phenotype; and

11           (e) identifying, in cells that exhibit the selected phenotype, the gene or  
12 genes whose expression is modulated by expression of a zinc finger protein, wherein the  
13 gene so identified is associated with the selected phenotype.

1           2. The method of claim 1, wherein the zinc finger protein has three,  
2 four, or five fingers.

1           3. The method of claim 1, wherein the library comprises no more than  
2  $10^7$  clones.

1           4. The method of claim 1, wherein the cells are physically separated,  
2 individual pools of cells and each individual pool of cells is transduced with an  
3 expression vector comprising a nucleotide sequence from the library.

1           5. The method of claim 4, wherein the physical separation of the  
2 pools of cells is accomplished by placing each pool of cells in a separate well of a 96,  
3 384, or 1536 well plate.

1           6. The method of claim 4, wherein the cells are assayed for the  
2 selected phenotype using liquid handling robots.

1           7. The method of claim 1, wherein the cells are pooled together and  
2 transduced in a batch.

1                   8.        The method of claim 7, wherein the cells are assayed for the  
2 selected phenotype using flow cytometry.

1                   9.        The method of claim 1, wherein the library is made by finger  
2 grafting, DNA shuffling, or codon doping.

1                   10.      The method of claim 1, wherein the zinc finger proteins are fusion  
2 proteins comprising a regulatory domain.

1                   11.      The method of claim 10, wherein the zinc finger proteins are fusion  
2 proteins comprising at least two regulatory domains.

1                   12.      The method of claim 10, wherein the regulatory domain is selected  
2 from the group consisting of a transcriptional repressor, a methyl transferase, a  
3 transcriptional activator, a histone acetyltransferase, and a histone deacetylase.

1                   13.      The method of claim 10, wherein the regulatory domain is VP16 or  
2 KRAB.

1                   14.      The method of claim 1, wherein modulation of gene expression is  
2 repression of gene expression.

1                   15.      The method of claim 1, wherein modulation of gene expression is  
2 activation of gene expression.

1                   16.      The method of claim 1, wherein the cells are selected from the  
2 group consisting of animal cells, plant cells, bacterial cells, protozoal cells, or fungal  
3 cells.

1                   17.      The method of claim 1, wherein the cells are mammalian cells.

1                   18.      The method of claim 1, wherein the cells are human cells.

1                   19.      The method of claim 1, wherein expression of the zinc finger  
2 proteins is controlled by administration of a small molecule.

1                   20.      The method of claim 19, wherein the small molecule is  
2 tetracycline.

1                   21. The method of claim 1, wherein the expression vectors are a viral  
2                   vector.

1                   22. The method of claim 21, wherein the expression vectors are a  
2                   retroviral expression vector, a lentiviral expression vector, an adenoviral expression  
3                   vector, or an AAV expression vector.

1                   23. The method of claim 1, wherein the selected phenotype is related to  
2                   cancer, nephritis, prostate hypertrophy, hematopoiesis, osteoporosis, obesity, or diabetes.

1                   24. The method of claim 1, wherein the zinc finger proteins comprise a  
2                   Zif268 backbone.

1                   25. The method of claim 1, wherein genes that are suspected of being  
2                   associated with the selected phenotype are identified by comparing differential gene  
3                   expression patterns in the presence and absence of expression of the zinc finger protein.

1                   26. The method of claim 25, wherein differential gene expression  
2                   patterns are compared using an oligonucleotide array.

1                   27. The method of claim 1, wherein genes that are suspected of being  
2                   associated with the selected phenotype are identified by using zinc finger proteins from  
3                   the library of randomized zinc finger proteins to probe YAC or BAC clones.

1                   28. The method of claim 1, wherein genes that are suspected of being  
2                   associated with the selected phenotype are identified by scanning genomic sequences for  
3                   target sequences recognized by zinc finger proteins from the library of randomized zinc  
4                   finger proteins.